

Report

Chronic idiopathic erythroderma of elderly men is an independent entity that has a distinct TARC/IgE profile from adult atopic dermatitis

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Abstract

Background Although there are several diseases that cause erythroderma, patients are often encountered with erythroderma of unknown cause which persists for a long time. The aim of this study was to characterize this chronic idiopathic erythroderma (CIE).

Methods Adult patients with CIE, atopic dermatitis (AD), psoriatic erythroderma (PsE), or generalized drug eruption (DE), who visited Fukuoka University Hospital Dermatology Department from 2010 to 2015, were enrolled. Their clinical and laboratory data were extracted from the patient database. CIE was defined as erythroderma without any apparent cause and lasting more than 3 months.

Results Twenty-three CIE, 82 AD, 39 psoriatic erythroderma, and 99 drug eruption cases were enrolled. The mean age of CIE patients was 74.7 ± 8.8 , and the male : female ratio was 21 : 2. Laboratory data for CIE and AD were similar, but serum levels of thymus and activation-regulated chemokine (TARC), a T-helper (Th) 2 cytokine, in the CIE group were significantly more elevated than in the AD group. Conversely, serum immunoglobulin (Ig) E levels were significantly lower in CIE patients compared with the atopic dermatitis group, and the ROC curve of the TARC/IgE ratio (7.24) provided efficient differentiation of the CIE group from AD patients. About PsE and DE, significant elevation of C-reactive protein was observed. Aspartate aminotransferase and alanine aminotransferase were also elevated in DE.

Conclusions Chronic idiopathic erythroderma is an independent condition which is likely to occur in elderly men. Immunity is shifted to the Th2 type in CIE; however, the mechanism may differ from that of atopic dermatitis.

Introduction

Erythroderma is characterized by diffuse erythema of the skin accompanied by a variable degree of scaling involving over 90% of the body surface.

Various diseases cause erythroderma, including eczema, atopic dermatitis, psoriasis, rashes induced by drugs or viral infection, Sezary syndrome, and cutaneous lymphomas such as mycosis fungoides. However, dermatologists often encounter erythrodermic cases of unknown etiology and, in approximately 30% of erythroderma patients, there is no underlying cause.¹ Papuloerythroderma of Ofuji is a representative erythroderma of unknown cause often seen in elderly men.^{2–5} It exhibits the characteristic clinical finding that papules and erythema fuse and expand to involve the whole body and become erythrodermic, but the erythema avoids skin folds, the so-called “deck chair sign.” However, patients with erythroderma of unknown cause do not necessarily conform to this clinical manifestation.

Typically, such idiopathic erythroderma is frequently seen in elderly men. However, we do not know whether this senile

erythroderma represents an independent disease entity. In previous studies,^{1,3} senile erythroderma patients were shown to have elevated levels of serum immunoglobulin (Ig) E and thymus and activation-regulated chemokine (TARC). Patients with atopic dermatitis (AD) are also well known to have elevated IgE and TARC.⁶ These common findings provoke the question of whether the pathophysiology of senile erythroderma is similar to AD.

To examine whether senile erythroderma is an independent entity, we compared clinical/biochemical characteristics of diseases that cause erythroderma, namely, typical AD, psoriatic erythroderma (PsE), and generalized drug eruption (DE).

Methods**Patients**

This was a retrospective cross-sectional study. Among patients who visited the Department of Dermatology, Fukuoka University Hospital, between January 2010 and December 2015, clinical data for those diagnosed as having erythroderma were

extracted from the patient database. Medical records of patients were manually checked, and those whose erythroderma continued for more than 3 months without any known cause were designated as suffering from chronic idiopathic erythroderma (CIE). Patients with obvious evidence of cutaneous lymphoma (adult T-cell lymphoma, mycosis fungoides, Sezary syndrome, or anaplastic large-cell lymphoma) were excluded. Patients with a medical history of AD or with obvious eczema lesions were also excluded from the CIE group.

To outline the characteristics of CIE, patients with adult AD, PsE, and DE were included as controls. For each disease, clinical data of patients older than 18 years were extracted in a similar manner from the database, and the diagnosis was confirmed manually by referring to the medical record. Patients with AD were enrolled only with a clinically typical manifestation that fulfills the criteria of Hanifin and Rajka, and with blood test results. Patients with PsE were diagnosed by clinical manifestation and histopathological examination. For DE, patients with toxic epidermolytic necrolysis and Stevens–Johnson syndrome were excluded, and we enrolled only patients with clinical manifestations of the disseminated papuloerythematous type of DE, confirmed by histopathological examination.

Blood tests

Data describing hematologic and biochemical tests undertaken at the patient's first visit were used.

Statistical analysis

Statistical analysis was carried out using SPSS. For comparison between two groups, Student's *t* test was used for continuous changes and the Mann-Whitney *U* test was applied for nonparametric variables. The significance level was set at $P < 0.05$. Correlations between variables were analyzed by Spearman's rank correlation analysis. A correlation coefficient, *r*, of less than 0.2 was considered as no correlation, 0.2–0.4 as a weak correlation, 0.4–0.6 as moderate, 0.6–0.8 as strong, and 0.8 or greater as an extremely strong correlation. This research was approved by the ethical committee of Fukuoka University School of Medicine.

Results

Profiles of patients (Table 1)

There were 23 patients (21 men, 2 women, male/female ratio = 10.5) in the CIE group. The mean age of CIE patients was 74.7 years old. Complications of malignant tumors were found in 7 of 23 CIE patients (30.4%), all of which were men. There was one case with a history of gastric cancer that was completely resected without recurrence, two cases of completely resected colorectal cancer without recurrence, one case with colorectal cancer whose erythroderma was improved after

Table 1 Patients' backgrounds

Disease groups	CIE	AD	PsE	DE
Numbers	23	82	39	99
Men/women	21/2	53/29	29/10	51/48
Mean age $\pm$ SD	74.7 $\pm$ 8.8	33.0 $\pm$ 14.5	57.5 $\pm$ 14.2	64.5 $\pm$ 14.9
Body mass index	21.7 $\pm$ 2.6	23.0 $\pm$ 4.0	23.8 $\pm$ 3.8	21.7 $\pm$ 4.4

CIE, chronic idiopathic erythroderma; AD, atopic dermatitis; PsE, psoriatic erythroderma; DE, drug eruption; SD, standard deviation.

surgical removal of the cancer, one case with a history of both gastric and esophageal cancers that were successfully treated, one case with a renal pelvis carcinoma and a past history of both gastric and esophageal cancer, and one case with a well-differentiated liposarcoma and a history of colon cancer. With respect to clinical manifestation, erythema that avoided skin folds of the abdomen, axilla, and popliteal fossa was observed in 8 of the 23 patients (34.8%), which is a characteristic manifestation of papuloerythroderma known as the deck chair sign.

Among the controls, there were 82 subjects (53 men, 29 women) in the AD group, 39 (29 men, 10 women) in the PsE group, and 99 in the DE group (51 men, 48 women). The male/female ratio was clearly higher in the CIE group than in the AD and DE groups ($P = 0.018$, $P < 0.001$, respectively, using Fisher's exact test), but there was no significant difference between the CIE and PsE groups ($P = 0.182$, Fisher's exact test). The mean age of subjects in the CIE group was significantly higher than in the AD, PsE, and DE groups combined ($P < 0.001$). Thus, CIE developed more frequently in elderly men.

Blood test results (Table 2)

Next, we compared the hematological and biochemical findings between the groups. There was no significant difference in the mean white blood cell count of the CIE group compared with the AD and PsE groups ($P = 0.367$ and $P = 0.428$, respectively), but the count was higher compared with the DE group ($P = 0.008$). The eosinophil count was highest in CIE ($1,088 \pm 926$) and was significantly higher than that in PsE and DE groups ($P = 0.002$ for both comparisons) but was not significantly different from that in AD patients ($P = 0.108$).

Aspartate aminotransferase and alanine aminotransferase levels were highest in the DE group (33.5 ± 31.7 IU/L and 35.9 ± 44.3 IU/L, respectively) and were significantly higher than those of the CIE group ($P = 0.007$ and $P = 0.012$, respectively). Lactate dehydrogenase (LDH) was highest in CIE patients (309.1 ± 82.8 IU/L) and was significantly higher than in the PsE and DE groups ($P = 0.027$ and $P = 0.04$, respectively) but not significantly different from AD patients ($P = 0.314$).

Table 2 Results of blood tests

	CIE		AD		PsE		DE	
	Mean	n	Mean	n	Mean	n	Mean	n
WBC/ μ l	8,600 $\pm$ 2,800	23	8,100 $\pm$ 2,400	80	9,300 $\pm$ 3,800	37	6,700 $\pm$ 3,100	98
Eosinophils/ μ l	1,088 $\pm$ 926	22	811 $\pm$ 637	78	338 $\pm$ 687	33	358 $\pm$ 525	90
AST (IU/l)	24.1 $\pm$ 5.1	23	24.6 $\pm$ 11.2	73	28.1 $\pm$ 19.0	37	33.5 $\pm$ 31.7	93
ALT (IU/l)	22.8 $\pm$ 10.7	23	26.2 $\pm$ 24.1	73	22.8 $\pm$ 11.1	37	35.9 $\pm$ 44.3	93
LDH (IU/l)	309.1 $\pm$ 82.8	23	286.0 $\pm$ 99.1	74	254.4 $\pm$ 95.0	37	254.1 $\pm$ 120.0	92
CRP (mg/dl)	0.67 $\pm$ 1.11	21	0.71 $\pm$ 1.98	56	2.90 $\pm$ 5.40	32	2.49 $\pm$ 3.87	89
IgE (IU/ml)	2,374 $\pm$ 4,983	17	10,000 $\pm$ 14,820	82	2,009 $\pm$ 2,039	13	829 $\pm$ 1,712	19
TARC (pg/ml)	15,888 $\pm$ 15,344	17	4,420 $\pm$ 6,990	80	9,735 $\pm$ 16,936	6	9,222 $\pm$ 16,275	10

All data are shown as mean $\pm$ SD.

CIE, chronic idiopathic erythroderma; AD, atopic dermatitis; PsE, psoriatic erythroderma; DE, drug eruption; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine.

The mean C-reactive protein (CRP) level was higher in the PsE (2.90 $\pm$ 5.40 mg/dl) and DE groups (2.49 $\pm$ 3.87 mg/dl) but was only slightly increased in the CIE (0.67 $\pm$ 1.11 mg/dl) and AD groups (0.71 $\pm$ 1.98 mg/dl). The mean CRP value was significantly lower in the CIE group compared with the PsE ($P = 0.03$) and DE groups ($P < 0.001$), and there was no significant difference compared with AD patients ($P = 0.932$).

Serum IgE levels were highest in the AD group (10,000 $\pm$ 14,820 IU/ml). The IgE values of the CIE group were significantly lower than those of the AD group ($P < 0.001$), and there was no significant difference compared with the PsE and DE groups ($P = 0.806$, 0.239, respectively).

The mean TARC level was highest in the CIE group (15,888 $\pm$ 15,344 pg/ml) and was significantly higher than in the AD group ($P = 0.008$), but there was no significant difference compared with the PsE and DE groups ($P = 0.42$ and $P = 0.296$, respectively) due to the limited number of samples.

From the results shown in Table 2, only IgE and TARC levels were significantly different between AD and CIE patients. A moderate correlation between IgE and TARC was observed in the AD group ($r = 0.592$, $P < 0.001$). Conversely, there was no significant correlation between IgE and TARC in the CIE group ($r = 0.415$, $P = 0.124$). When the IgE–TARC relationships in the CIE and AD groups were plotted on a graph, the CIE patients clustered in a low IgE–high TARC area compared with the AD patients (Fig. 1). Because the TARC/IgE (T/E) ratio of AD and CIE was different, we used this ratio as a distinction marker for CIE. The ROC curve of the T/E ratio (Fig. 2) showed an area under the curve of 0.918 (standard error = 0.042, 95% confidential interval 0.834–1.000). We determined the cut-off value as the point closest to 1-specificity of 0 and sensitivity of 1 on the ROC curve. The T/E ratio could successfully distinguish CIE from AD with a sensitivity of 80% and specificity of 95% when the T/E ratio was >7.24 .

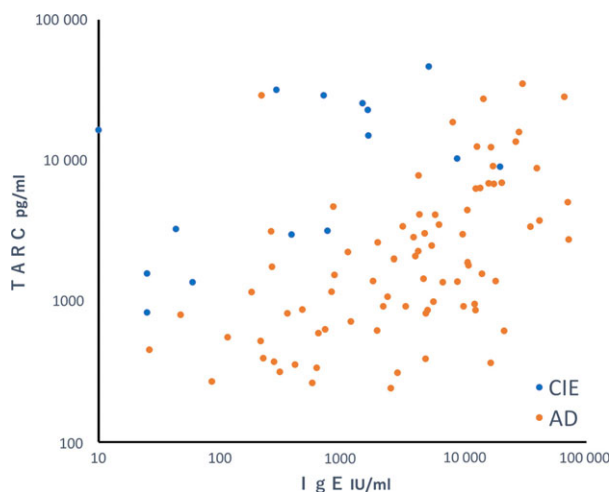


Figure 1 Correlation between IgE and TARC in CIE and AD. IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine; CIE, chronic idiopathic erythroderma; AD, atopic dermatitis

Discussion

Adult AD is considered to be an important disease for the differential diagnosis of CIE. AD is a chronic dermatitis which is frequent in children, accompanied by deterioration of epidermal barrier function, and characteristically associated with increases in serum IgE and TARC levels.⁶ The pathogenesis of AD is thought to involve a patient's immunity shifting to the Th2 type, and patients with AD often have allergic diseases such as asthma and allergic rhinitis.⁷ It is considered that AD is most common in children and prevalence decreases in adults, with many cases of natural remission. We selected typical adult AD patients with a history from childhood as one of the comparator disease groups for CIE.

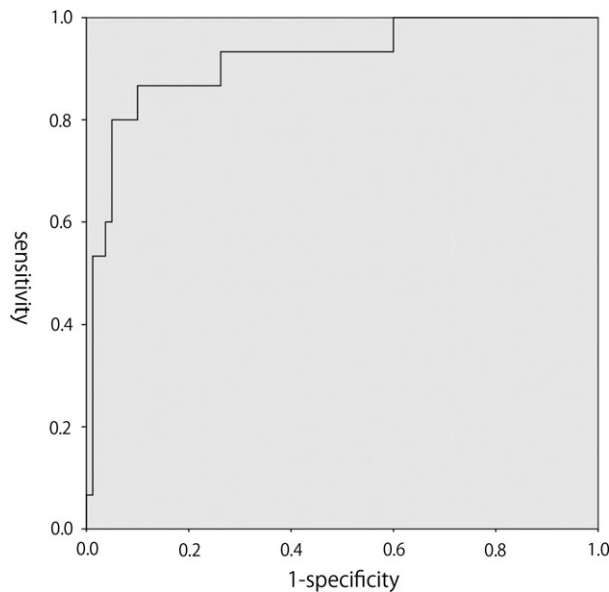


Figure 2 ROC curve of TARC/IgE ratio which distinguishes CIE from AD. Cut-off value of 7.24 provides sensitivity of 80% and specificity of 95%. IgE, immunoglobulin E; TARC, thymus and activation-regulated chemokine; CIE, chronic idiopathic erythroderma; AD, atopic dermatitis

TARC (also known as chemokine (C-C motif) ligand 17) is a cytokine produced by cells such as keratinocytes, dendritic cells, vascular endothelial cells, and platelets.⁶ In particular, TARC is produced by dermal dendritic cells following stimulation by thymic stromal lymphopoietin and causes Th2 cells to migrate to the skin.⁸ Serum levels of TARC closely reflect the severity of AD, and rise when AD is exacerbated.^{3,6} On the other hand, IgE is an immunoglobulin involved in type 1 allergic reactions. Antigen-specific IgE binds to mast cells and basophils, inducing them to release mediators such as histamine in response to antigen stimulation. In a report of 169 AD patients followed for 4 years,⁹ a lower frequency of improved subjects (14.3%) was seen in a group with high IgE (>10,000 IU/mL), whereas a higher frequency (79.7%) was seen in a low IgE group (<1,000 IU/mL).

We observed that IgE and TARC were elevated in patients of both CIE and AD groups, as previously reported.¹ However, the relationship between IgE and TARC was different in the two diseases, and the T/E ratio (>7.24) efficiently differentiated CIE from AD. This observation has not been previously reported and may prove that the two conditions are indeed independent of one another. One possibility remains that the T/E ratio is dependent on age. Because CIE occurs almost exclusively to the elderly men as one of the important features of the disease, we could not compare data in the same age groups. When we analyzed the correlation between age and IgE, TARC, and T/E ratio in patients with AD, we found no correlation between age and IgE ($r = -0.15$, $P = 0.179$), age and TARC ($r = 0.092$, $P = 0.416$), however, T/E ratio showed minimal correlation with

age ($r = 0.236$, $P = 0.035$). Therefore, age could be one of the factors that causes a difference. However, the T/E ratio of AD and CIE differed greatly, so we assume that characteristics of the disease cause the difference rather than age.

The mechanism leading to the observed difference between CIE and AD T/E ratio is not yet understood. One clue is that many AD patients have barrier abnormalities in the skin,¹⁰ which eventually leads to IgE production against exogenous environmental antigens.¹¹ Inherent barrier abnormalities are unlikely in CIE, so erythroderma may be occurring endogenously. In the elderly, the number of induced regulatory T cells decreases with age, which may lead to low-grade and chronic inflammation.¹²

Another reason for endogenous erythroderma may be the tumor-bearing condition of the patients. Several patients with erythroderma complicated by a malignant tumor have been reported,⁴ and erythroderma has become recognized as a dermatome that is associated with tumors. In our CIE group, 7 of 23 patients (30.4%) had cancer complications. However, the average age of patients in the CIE group was 75 years old; therefore, it was undetermined whether this rate of cancer was particularly high. There are many cases in which there is no longitudinal correlation between the time of cancer diagnosis and the time of onset of erythroderma, so it cannot be asserted that a malignant tumor is the cause of the erythroderma.

In the CIE patients, LDH was correlated with TARC ($r = 0.539$, $P = 0.026$). Therefore, in CIE, similar to AD, we infer that LDH is released from keratinocytes in response to chronic dermatitis. Also, the CRP levels of patients with CIE were not elevated, while those of PsE and DE patients were increased. Patients with psoriasis commonly have chronically elevated CRP,^{13,14} and in psoriatic arthritis, CRP becomes higher.¹³ With DE, the effects of the original disease for which the drugs were administered or drug-induced hepatitis, may be responsible for the elevated CRP levels.

In summary, we found that (i) patients in the CIE group were mostly elderly men of significantly greater age than patients in the other groups; (ii) the biochemical data indicate that IgE and TARC were elevated in both the CIE and AD groups. Furthermore, these two groups both had lower CRP and higher LDH compared with the PsE and DE patient groups; (iii) in the CIE group, serum IgE was not elevated to the same extent as in AD patients, but conversely, TARC was higher. IgE and TARC correlated well in the AD group; however, this correlation was not seen in the CIE group. The ROC curve of the T/E ratio suggests that CIE can be distinguished from AD with a sensitivity of 80% and specificity of 95% when the T/E ratio is >7.24.

Limitations of this study are the relatively small sample size and the fact that it was undertaken in a single facility. Blood biochemical examinations were not performed in all cases. In some patients, treatment had already been started in other medical institutions. Ages of patient groups were different, which may have affected the biochemical results.

We conclude that CIE is a condition likely to occur in elderly men and shows a high T/E ratio profile distinct from AD

patients. In the future, further research is necessary that incorporates larger sample sizes and evaluation of a wider panel of cytokines in addition to TARC.

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